Pathophysiology and therapeutic options for cirrhotic portal hypertension

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Portal hypertension represents the primary non-neoplastic complication of liver cirrhosis and has life-threatening consequences, such as oesophageal variceal bleeding, ascites, and hepatic encephalopathy. Portal hypertension occurs due to increased resistance of the cirrhotic liver vasculature to portal blood flow and is further aggravated by the hyperdynamic circulatory syndrome. Existing knowledge indicates that the profibrogenic phenotype acquired by sinusoidal cells is the initial factor leading to increased hepatic vascular tone and fibrosis, which cause increased vascular resistance and portal hypertension. Data also suggest that the phenotype of hepatic cells could be further impaired due to the altered mechanical properties of the cirrhotic liver itself, creating a deleterious cycle that worsens portal hypertension in the advanced stages of liver disease. In this Review, we discuss recent discoveries in the pathophysiology and treatment of cirrhotic portal hypertension, a condition with few pharmacological treatment options.

Introduction

Incidence of cirrhosis and portal hypertension

Portal hypertension is the primary clinical complication of cirrhosis and can lead to hepatic decompensation and death. In 2019, cirrhosis was accountable for 2·4% of global deaths, being one of the leading causes of mortality, with an age-standardised global prevalence of 1·4%.[1] Cirrhosis is considered the end stage of chronic liver disease, which has different aetiologies, the main ones being viral hepatitis and steatotic liver disease. Although viral hepatitis is still the main cause of chronic liver disease, the development of new direct-acting antivirals alongside the escalating global incidence of obesity that has recently boosted the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) mean that the epidemiology of chronic liver disease is changing.[1] Projections suggest a forthcoming surge in MASLD-related cirrhosis in the upcoming years.[2,3] Despite occurring less frequently, portal hypertension can also manifest in chronic liver disease independently of cirrhosis,[4] or can arise as a result of pre-hepatic and post-hepatic obstructions to blood circulation.[5] Indeed, portal hypertension might occur in some instances preceeding cirrhosis, as is the case of porto-sinusoidal vascular disorder, which can affect the sinusoidal vascular tone independently of fibrosis.[6]

Intrahepatic vascular resistance

Cirrhotic portal hypertension is the direct consequence of increased intrahepatic vascular resistance to blood flow, as defined by Ohm's law.[7] Prolonged liver damage triggers a cascade of structural and dynamic alterations that disrupt the hepatic microcirculation and, consequently, these changes are the primary instigators of portal hypertension during progression of chronic liver disease (figure 1). Understanding the mechanisms driving this sequence of events becomes pivotal in the pursuit of preventing or devising treatments for portal hypertension. Although the exact mechanisms linking each cause of chronic liver disease to increased intrahepatic vascular resistance remain incompletely understood and might differ, a widely accepted notion is that chronic damage leads to hepatotoxicity and cell death that results in increased hepatic inflammation and microvascular dysfunction.[8] The perpetuation of this scenario would then prompt the activation of hepatic stellate cells (HSCs), which adopt a pro-contractile and profibrogenic phenotype.[9] These processes have two core implications. First, the contraction of activated HSCs, supported by vasoconstrictors produced by the dysfunctional sinusoidal endothelium, culminates in a reduction of the sinusoidal diameter and, according to the Hagan–Poiseuille equation, the elevation of hepatic vascular tone, which is the dynamic component of intrahepatic vascular resistance. Second, chronically activated HSCs synthesise and release extracellular matrix components, commencing with perisinusoidal fibrosis and culminating in nodular fibrosis in advanced stages.[10] The formation of this scar tissue evolves into a physical obstruction for liver microcirculation, and is considered the structural component of intrahepatic vascular resistance. It is widely acknowledged that both these dynamic and structural hepatic modifications substantially contribute to elevated intrahepatic vascular resistance, with respective contributions of approximately 40% and 60%.[7,11] Notably, beyond their direct influence on intrahepatic vascular resistance, hepatic microcirculatory alterations also modify the mechanical properties of the liver, consequently compromising the phenotype of primary hepatic cell types.[12] Indeed, pathologic changes in liver stiffness, shear stress, or vascular stretching have been described to negatively affect the phenotype of most hepatic cell types, as liver cells are able to respond to the mechanical properties of the environment.[12]

Hyperdynamic circulation

As intrahepatic vascular resistance increases, the splanchnic region develops elevated blood pressure and, consequently, the splanchnic endothelium releases

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vasodilators as a countermeasure to this hypertension. However, in the context of advanced chronic liver disease, the liver's responsiveness to vasodilators is blunted. Consequently, the continuous release of vasodilators within the splanchnic region leads to mesenteric and systemic vasodilation instead. This vasodilation, in turn, results in a decline in mean arterial pressure and the onset of effective hypovolaemia. In response, the heart accelerates its cardiac output to compensate for the reduced pressure, while the kidneys retain sodium and water to augment blood volume (and systemic pressure). Collectively, these adjustments culminate in an elevation of hepatic portal blood flow, which, as per definition by Ohm's law, constitutes an additional factor that augments portal pressure.[13] Hence, in the advanced stages of chronic liver disease, portal hypertension emerges as a consequence of both intrahepatic vascular resistance and the hyperdynamic circulatory syndrome (figure 1).

The fact that the hyperdynamic circulatory system contributes to portal hypertension lays the foundation for the use of non-selective β blockers (NSBBs) and other systemic vasoconstrictor agents in the management of portal hypertension. Although these treatments are some of the most potent pharmacological interventions for mitigating portal hypertension, it is important to note that therapies designed to address the hyperdynamic circulatory syndrome can merely offer a partial reduction in portal pressure. This limitation arises from the fact that the primary driver of portal hypertension in chronic liver disease remains the increased intrahepatic vascular resistance.

Clinical definition and complications of portal hypertension

In humans, portal hypertension is clinically defined as a hepatic venous pressure gradient (HVPG) of 5 mm Hg or greater.[14] However, it is at HVPG values of 10 mm Hg or greater, termed clinically significant portal hypertension (CSPH), where the potential for clinical complications arises.[15] In the context of CSPH, the prolonged increase in cardiac output can lead to chronic cardiac dysfunction, and the rise in blood volume due to sodium retention can result in ascites development. Portal hypertension can also induce splanchnic angiogenesis, leading to the formation of collateral vessels. These veins act as a pathophysiological solution to portal hypertension, allowing some blood flow to bypass the liver. This diversion prevents ammonia and other blood components from being metabolised in the liver, reducing systemic blood detoxification and contributing to the development of hepatic encephalopathy.[16] Collateral veins in the oesophagus or stomach are termed oesophageal or gastric varices. These varices have thin and immature walls due to elevated pressure and immature development, making them prone to rupture. This rupture can lead to variceal bleeding, a major cause of mortality, especially when HVPG values are 12 mm Hg or greater. The interplay of these complications, along with microcirculatory dysfunction within the hepatic domain, can predispose individuals to acute-on-chronic liver failure. Reducing HVPG to less than 12 mm Hg or by at least 20% compared with baseline,[14] either by intrahepatic or systemic treatment, decreases the risk of decompensation and death.[16]

Concerns have been raised regarding whether thresholds defining CSPH are accurate for burgeoning causes of cirrhotic portal hypertension, especially steatosis. Steatosis entails the accumulation of lipids, leading to an augmentation in hepatocyte volume, and is hypothesised to increase intrahepatic vascular resistance by obstructing the sinusoids, potentially as a standalone cause of portal hypertension. Two distinct studies that evaluated this hypothesis reported no significant incidence of portal hypertension in patients with MASLD without cirrhosis, suggesting that steatosis alone does not induce increased intrahepatic vascular resistance and portal hypertension.[17,18] One study found that hepatic steatosis did not impact HVPG in a cohort of mostly patients with chronic liver disease and cirrhosis, but advises caution as steatosis might artificially increase liver stiffness measurements, which usually correlate with portal pressure and are usually complementary to HVPG measurements.[17] Furthermore, a cross-sectional study found that patients with advanced MASLD (defined as patients with both MASLD and advanced stage 3 or 4 fibrosis or portal hypertension) showed a higher prevalence of portal hypertension-related decompensation than did patients with virally active (hepatitis C virus positive viraemia) advanced chronic liver disease with portal hypertension.[19] Similarly, a retrospective analysis of patients with CLD and CSPH revealed that 14 (16%) of 89 did not have cirrhosis.[4] Most of the 16% of these patients without cirrhosis had MASLD or nodular regenerative hyperplasia, which is a characteristic condition in PSVD.[4,20] These studies suggest that the cause of chronic liver disease should be considered alongside HVPG for the definition of decompensation risks.

Therapeutic approaches for portal hypertension

Over the past few decades, understanding of the mechanisms underlying the development of portal hypertension has progressed considerably. Despite advances in the management of cirrhosis,[10] the primary approach for the treatment of cirrhosis remains the removal of the causal agent, surgical intervention, or use of a limited number of pharmacological strategies that primarily address the complications of portal hypertension.[21,22]

Targeting the causal agent

The course of chronic liver disease can span from mild fibrosis to cirrhosis, with cirrhosis progressing from a compensated phase to a decompensated phase. These

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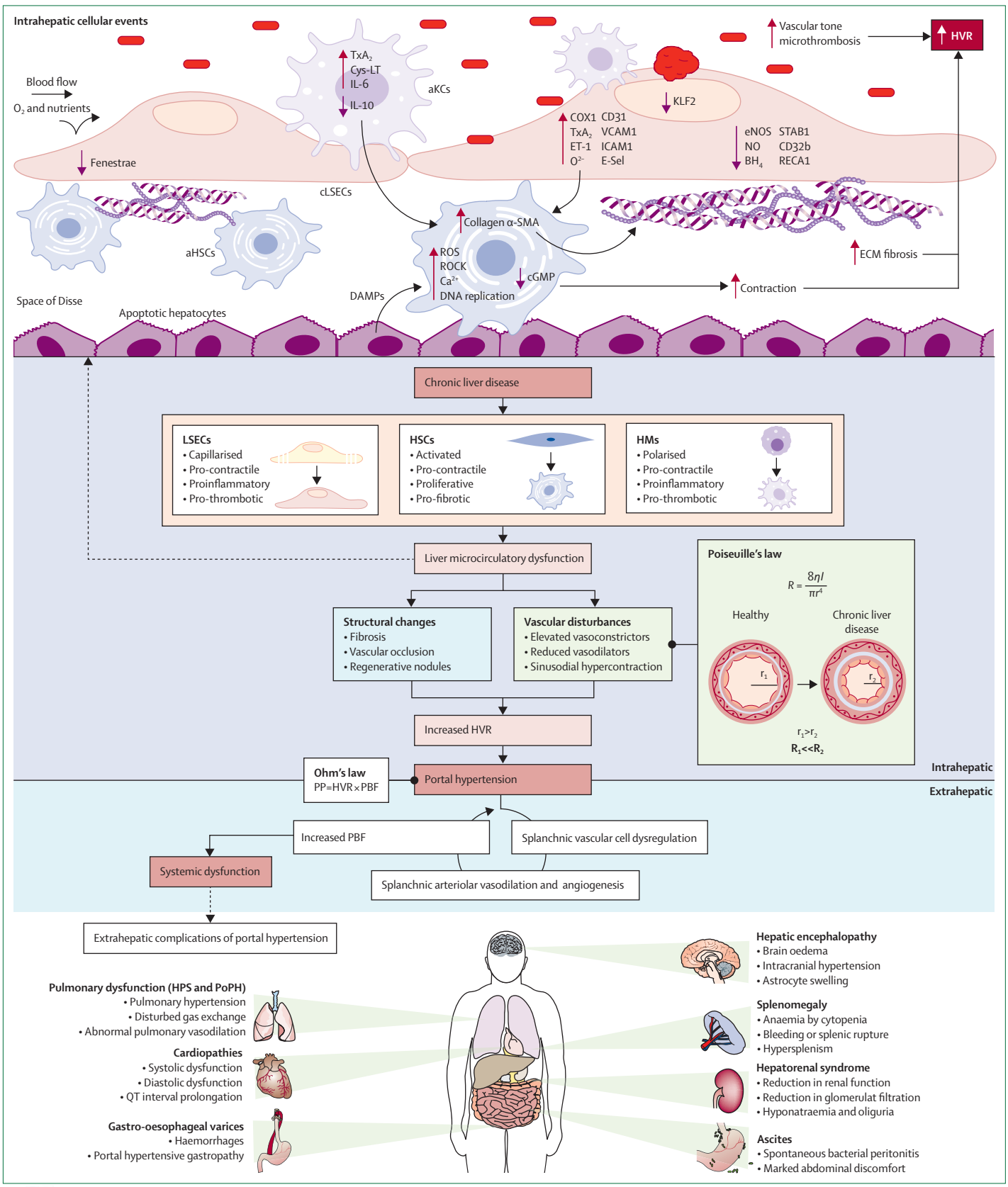

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phases exhibit variations in clinical presentation, outcomes, mortality rates, and predictors of death. Decompensation is defined by the appearance of clinical complications of portal hypertension, including ascites, bleeding from gastro-oesophageal varices, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy. Understanding the pathophysiological mechanisms underlying the progression through these stages is crucial for the contemporary management of chronic liver disease and for achieving disease regression.[23] In this regard, a certain degree of spontaneous regression of cirrhosis, and consequently portal hypertension, has been observed in different preclinical models of advanced chronic liver disease after cessation of the injuring agent.[24–29] Indeed, the reversion of portal hypertension is closely related to the reduction of intrahepatic vascular resistance due to changes in the structural and dynamic components of the liver after removal of the causative agent.[30,31] In humans, however, it has been suggested that, at a certain point in the progression of chronic liver disease, specifically in decompensated chronic liver disease, the cellular and architectural changes in the liver are so profound that the disease becomes irreversible even after removal of the causal factor.[32] Nevertheless, data from patients cured of viral hepatitis suggest that a proportion of patients with advanced fibrosis and cirrhosis have disease regression with antiviral treatment, showing improved HVPG and liver histology.[33,34] Additionally, in contrast to the previously held belief that the transition from compensated to decompensated cirrhosis was irreversible, recent findings on disease regression indicate that some patients with decompensated chronic liver disease can undergo reversal—hepatic recompensation—following the suppression or cure of the underlying cause.[35] Nevertheless, reports also indicate that livers with regressed chronic liver disease are more prone to the prompt development of chronic liver disease when exposed to additional injury, such as MASLD.[36] Despite phenotypical regression, some mechanisms might not be fully reverted and could be in a ready state, prone to reactivation.

Notwithstanding, some positive data regarding spontaneous regression of portal hypertension and chronic liver disease, it is important to highlight that the proportion of patients whose disease does not regress or even progresses after removal of the causal agent remains considerable.[21] Hence, finding a therapy for portal hypertension, which might be additional to spontaneous regression (ie, could be concomitantly given with agents treating the causal factor), still represents an unmet clinical need. In this regard, finding predictors of portal hypertension regression outside of HVPG would facilitate the identification of regression and the evaluation of the efficacy of novel therapies.[37] Among predictors, a reduction in the mean diameter of the largest collateral vessel,[38] the absence of large collateral vessels (>9 mm),[39] a reduction of liver and spleen stiffness,[40,41] novel extracellular matrix serological biomarkers known as neoepitopes (pro-collagen III, collagen IV marker, collagen V marker, and elastin),[42] and a lower MELD score[43] might be helpful in this regard.

Pharmacological interventions targeting extrahepatic alterations

Among the current pharmacological options for portal hypertension in chronic liver disease, systemic interventions are the most studied and currently used, aimed at improving the hyperdynamic circulatory syndrome. Therefore, the action of these systemic interventions is mostly independent of the cause of chronic liver disease,[44] targeting its complications rather than its pathophysiology.[10]

The most studied systemic pharmacological strategy to reduce portal hypertension is the use of NSBBs. NSBBs are inhibitors of the β1 adrenergic receptors predominantly found in the heart and the β2 adrenergic receptors largely found in vascular smooth muscle cells. Therefore, their inhibition leads to systemic vasoconstriction and a reduction of cardiac output, which in turn reduces portal blood flow and, consequently, portal hypertension. NSBBs are estimated to reduce portal pressure by about 15%.[45] This downregulation prevents complications of portal hypertension, such as primary and secondary bleeding from gastro-oesophageal varices, portal hypertensive gastropathy, ascites, and spontaneous bacterial peritonitis.[45] Moreover, NSBBs reliably prevent the decompensation of cirrhosis, although efficacy in early

Figure 1: **Portal hypertension pathophysiology**
Throughout the course of chronic liver disease, several key cellular changes occur within the liver. LSECs dedifferentiate into a capillarised state, HSCs become activated, and HMs undergo polarisation. These changes collectively contribute to the development of hepatic microcirculatory dysfunction. Hepatic architectural integrity becomes compromised, primarily as a result of the excessive production and deposition of ECM components, which subsequently leads to fibrosis. There is an increase in the hepatic vascular tone, driven by an upregulation in vasoconstrictor activity and diminished vasodilator capacity. Combined, these changes lead to increased HVR, the primary factor in the development of portal hypertension. In turn, splanchnic endothelial cells try to compensate this local increase in blood pressure by releasing vasodilators and inducing angiogenesis, causing systemic vasodilation and the formation of collateral vasculature circumventing the liver, further increasing PBF and aggravating portal hypertension. Systemic dysfunction from increased PBF and portal hypertension can precipitate the development of extrahepatic complications. α-SMA=α-smooth muscle actin. aHSCs=activated hepatic stellate cells. aKCs=activated Kupffer cells. BH_4=tetrahydrobiopterin. cGMP=cyclic GMP. cLSECs=capillarised liver sinusoidal endothelial cells. COX=cyclooxygenase. Cys-LT=cysteinyl leukotriene. DAMPs=damage-associated molecular patterns. ECM=extracellular matrix. eNOS=endothelial nitric oxide synthase. E-Sel=E-Selectin. ET-1=endothelin-1. HMs=hepatic macrophages. HPS=hepatopulmonary syndrome. HSCs=hepatic stellate cells. HVR=hepatic vascular resistance. ICAM1=intercellular adhesion molecule 1. KLF2=Krüppel-like factor 2. l=length of the vessel. LSECs=liver sinusoidal endothelial cells. NO=nitric oxide. PBF=portal blood flow. PoPH=portopulmonary hypertension. PP=portal pressure. R=resistance to flow. r=sinusoid radius. RECA1=rat endothelial cell antigen 1. ROCK=Rho-associated protein kinase. ROS=reactive oxygen species. STAB1=stabilin 1. TxA2=thromboxane A2. VCAM1=vascular cell adhesion molecule 1. η=blood viscosity.

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compensated cirrhosis is unclear as they do not improve patient overall survival or survial rates.[45] The PREDESCI trial showed that long-term treatment with NSBBs improved decompensation-free survival in patients with compensated cirrhosis and CSPH, primarily by reducing the occurrence of ascites.[46]

Carvedilol, a unique type of NSBB that displays additional α1 adrenergic effects, has the capacity to enhance nitric oxide release, and therefore has both extrahepatic and intrahepatic effects. Furthermore, a greater proportion of patients respond to carvedilol than to other NSBBs, such as propranolol, and the drug strongly reduces HVPG with a better tolerance and safety profile.[45] A meta-analysis of randomised controlled trials showed that long-term carvedilol treatment reduced decompensation of cirrhosis and significantly improved survival versus control therapy in patients with compensated cirrhosis and CSPH.[47] Although around 30% of patients present contraindications or side-effects due to NSBBs, their use is widely accepted because of their efficacy in cirrhosis, with the most prescribed NSBBs being propranolol, timolol, and nadolol.[45] The primary concern regarding the widespread use of carvedilol in patients with cirrhosis is its vasodilatory component. The anti-α1 adrenergic effect of carvedilol on systemic vascular resistance might lead to a

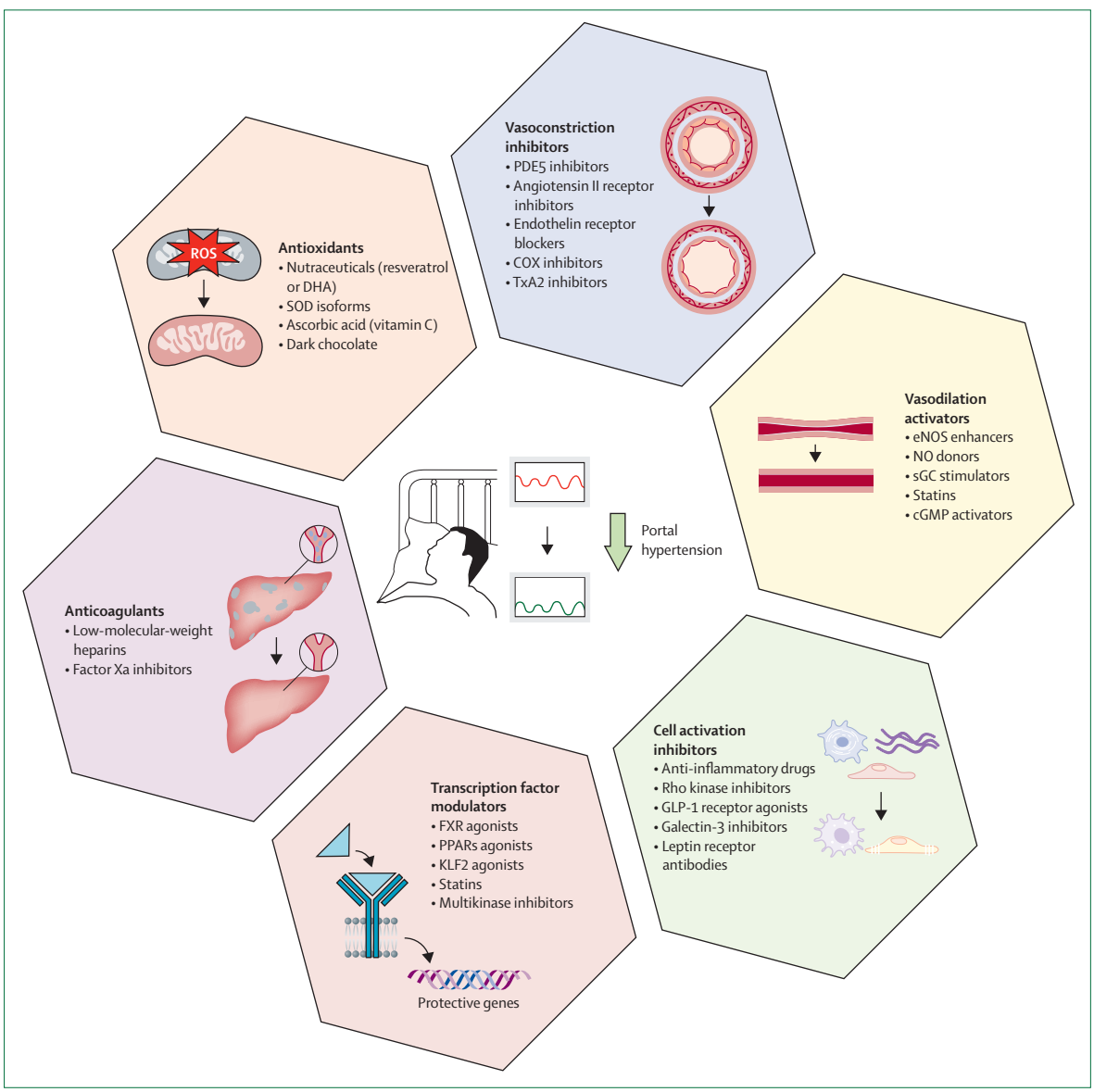

Figure 2: **Therapeutic approaches for portal hypertension**
cGMP=cyclic GMP. COX=cyclooxygenase. DHA=docosahexaenoic acid. eNOS=endothelial nitric oxide synthase. FXR=farnesoid X receptor. KLF2=Krüppel-like factor 2. NO=nitric oxide. PDE5=phosphodiesterase type 5. PPAR=peroxisome proliferator-activated receptor. sGC=soluble guanylate cyclase. SOD=superoxide dismutase. TxA2=thromboxane A2.

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larger reduction in arterial blood pressure compared with traditional NSBBs. A study involving a small number of patients showed that lower doses of carvedilol were well tolerated and resulted in a lesser reduction in systemic pressure versus higher doses while maintaining a similar decrease in HVPG.[48] In a study with 72 patients with cirrhosis, higher doses of carvedilol showed stronger effects on HVPG reduction (in patients that did not respond to the initial low dose).[49] Some of the patients treated with the high dose also displayed arterial hypotension.

Recommendations on the use of NSBBs were updated in the Baveno VII guidelines,[50] which underscored the importance of maintaining a mean arterial pressure of 65 mm Hg or more or a systolic arterial blood pressure of 90 mm Hg or more, and a heart rate of more than 55 beats per min during therapy.[45] These values correspond to the safety zone limits to optimise the beneficial effects of NSBBs in decompensated cirrhosis. In patients with ascites, especially those with refractory ascites who are more prone to having lower arterial pressure, the Baveno VII guidelines recommend considering dose reduction or discontinuation of traditional NSBBs or carvedilol in the presence of persistent arterial hypotension.

Pharmacological interventions targeting intrahepatic alterations

Increased intrahepatic vascular resistance is the primary factor in the development of portal hypertension. Therefore, the main focus of current research is therapies targeting liver microcirculation dysfunction and architecture distortion (fibrosis).[8] In the chronically diseased liver, a series of cellular dysregulations induce the procontractile state of the liver sinusoids, increasing resistance to blood flow. Additionally, chronic inflammation, endothelial dysfunction, HSC activation, parenchymal extinction, and other biomechanical alterations further dysregulate the sinusoidal milieu, leading to considerable architectural disturbances, which perpetuate and aggravate portal hypertension. Current guidelines do not specifically recommend any therapeutic approach targeting intrahepatic dysregulations in portal hypertension.[23,50] Nevertheless, different interventions have been proposed to target the dysfunctional cells of the liver sinusoid to reduce the vascular and structural alterations of the cirrhotic liver (figure 2; tables 1, 2).

Targeting transcription factors

One of the most well known and studied therapies for portal hypertension are statins. Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, an enzyme that participates in the synthesis of cholesterol. However, inhibition of this enzyme leads to the parallel inhibition of the isoprenylation of small GTPases and subsequent upregulation and activation of the vasoprotective transcription factor Krüppel-like factor 2 (KLF2) in endothelial and stellate cells. Through these vasoprotective, cholesterol-independent pathways, statins induce a profound change in sinusoidal cells phenotype, leading to the synthesis of nitric oxide[117] (a key vasodilator in the vasculature)[118,119] and deactivation of HSCs,[58,65] together inducing vasorelaxation and preventing vasoconstriction. Furthermore, statins induce an anti-inflammatory phenotype in the liver endothelium and reduce oxidative stress, blunting the progression of chronic liver disease overall and improving hepatic haemodynamics in animal models of cirrhosis, with further inhibitory effects on fibrogenesis.[89] These translational studies led to the clinical evaluation of statins, including proof-of-concept randomised and retrospective studies, which provide evidence for the use of statins in the treatment of cirrhosis and portal hypertension.[120]

The farnesoid X receptor (FXR) is a transcription factor that modulates bile acid and lipid metabolism. When FXR is dysregulated, it can trigger changes in bile acid homoeostasis and lipids, causing cholestatic injury, inflammation, and fibrosis in the liver. Accordingly, FXR agonists are considered a promising therapeutic treatment against chronic liver disease and portal hypertension. FXR activation stimulates endothelial nitric oxide synthase activity and nitric oxide production, which means that an FXR agonist might ameliorate portal hypertension and vascular remodelling.[57,121]

The peroxisome proliferator-activated receptor (PPAR) family—PPAR-α, PPAR-δ (also known as PPAR-β), and PPAR-γ—are nuclear receptor transcription factors implicated in the maintenance of liver homoeostasis and function. However, in liver disease, PPARs are downregulated, leading to inflammation, insulin resistance, and fibrogenesis.[122] Different studies have considered the use of PPAR agonists as potential therapies to improve sinusoidal cell phenotype, reverse liver fibrosis, reduce inflammation and steatosis, and consequently reduce portal hypertension.[55,67]

Nitric oxide modulators

A pharmaceutical strategy widely used in the research field of vascular biology is enhancing nitric oxide production and release to induce vasodilation.[123] The administration of nitric oxide donors as a therapy for portal hypertension has been tested in some clinical settings in the 1990s to 2000s, although not validated as a treatment. The aim of treatment was to reduce pressure in the porto-sinusoidal vascular system and prevent the associated complications, such as bleeding from oesophageal varices. However, the efficacy and safety of nitric oxide donor administration have been the subject of debate and study because of the undesired effects on the systemic circulation, such as systemic hypotension and renal dysfunction. Therefore, nitric oxide donor administration was abandoned and this strategy was no longer studied due to the absence of proven efficacy and

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	Drug	Mechanism	Administration method	Experimental model	Effects
Short duration					
Biecker et al (2008)[51]	AVE 9488	Nitric oxide enhancer	1·0 mg/day for 2 days	Male Sprague–Dawley cBDL-cirrhotic rats	Decreased portal pressure and HVR, and increased phosphorylated eNOS
Watanabe et al (2007)[52]	BQ-123	Endothelin A receptor antagonist	10 nmol/min infused via a catheter in the mesenteric vein for 10 min	Healthy male Wistar rats	Decreased portal pressure and increased number and diameter of fenestrae
Graupera et al (2003)[53]	Indomethacin, SC-560, and SQ-29548	COX-1 inhibitors and thromboxane A2 receptor antagonist	Indomethacin (20 μM) and SC-560 (5 μM) 15 min before and SQ-29548 (1 μM) 10 min before the study	Male Wistar CCl_4-cirrhotic rats	Increased vasodilatory response to acetylcholine, decreased thromboxane B2 production, and decreased endothelial dysfunction
Gracia-Sancho et al (2007)[54]	Furegrelate, SC-560, and SQ-29548	Inhibitors of the COX-1 and thromboxane A2 pathway	Furegrelate (50 mg/kg) 14 h before, SC-560 (5 μM) 15 min before, and SQ-29548 (1 μM) 10 min before the study	Male Wistar CCl_4-cirrhotic rats	Increased vasodilatory capacity, improved endothelial function, and decreased thromboxane B2 production
Boyer-Diaz et al (2021)[55]	Lanifibranor	Activation of PPARs by pan-PPAR agonist	1 μM, 3 μM, or 10 μM for 24 h in vitro	Primary human liver cells from patients with cirrhosis	Improved HSC phenotype and decreased HSC contraction capacity
Mesquita et al (2017)[56]	Liraglutide	GLP-1 receptor agonist	50 μM for 72 h in vitro	Primary human HSCs from patients with cirrhosis and immortalised human-activated HSC LX-2 cells	Decreased HSC activation, contraction capacity, and inflammation
Laleman et al (2007)[57]	Nitroflurbiprofen or flurbiprofen	Nitric oxide-releasing COX inhibitors	45 mg/kg or 30 mg/kg 24 h and 1 h before the experiments	Male Wistar thioacetamide-cirrhotic rats	Decreased portal pressure, splanchnic hyperaemia, HVR, and thromboxane B2
Marrone et al (2015)[58]	Simvastatin	KLF2 inducer	0·1 μM, 1 μM, and 10 μM for 24 h and 72 h in vitro	LX-2 cells and primary HSCs	Increased KLF2 and decreased α-SMA
La Mura et al (2013)[59]	Simvastatin	KLF2 inducer	25 mg/kg given 3 h and 23 h after lipopolysaccharide challenge	Male Wistar rats administered with lipopolysaccharide	Decreased portal pressure and LSEC dysfunction, and increased eNOS phosphorylation
Huang et al (2010)[60]	Simvastatin	KLF2 inducer	10 μM for 25 min	Male Sprague–Dawley rats with portal hypertension induced by PPVL	Decreased portal pressure and collateral vascular resistance; increased scavenger receptors, phosphorylated eNOS, COX-2, and thromboxane A2 expression
García-Calderó et al (2011)[61]	Tempol (SOD mimetic)	Antioxidant	180 μmol for 30 min	Male Wistar CCl_4-cirrhotic rats	Decreased portal pressure, HVR, and oxidative stress; increased nitric oxide
Uschner et al (2020)[62]	Udenafil	PDE5 inhibitor	1 mg/kg and 5 mg/kg for 60 min	Male Sprague–Dawley cBDL-cirrhotic or CCl_4-cirrhotic rats	Decreased portal pressure and HVR, and increased intrahepatic vasodilation, phosphorylated eNOS protein, and cGMP
El-Mezayen et al (2018)[63]	HSCs-targeting valsartan	Angiotensin II receptor antagonist	40 mg/kg	Male Wistar CCl_4-cirrhotic rats	Increased PPAR-γ and MAS receptor; decreased fibrosis, TGF-β, MMP-2, and hydroxyproline
Duong et al (2015)[64]	HSCs-targeting nitric oxide	Nitric oxide donor	250×10^{-6} M nanoparticles in vitro and 168 mg dissolved in 1 mL saline in vivo	Human LX-2 cells and rat HSCs in vitro and male Sprague–Dawley cBDL-cirrhotic rats in vivo	Decreased α-SMA, collagen I, endothelin-1, and CTGF in vitro; decreased portal pressure in vivo
Klein et al (2012)[65]	Y26732	Rho kinase inhibitor	Single dose of 0·05 mg/kg	Male Sprague–Dawley CCl_4-cirrhotic rats and cBDL-cirrhotic rats	Decreased portal pressure, and moesin expression and phosphorylation
Long duration					
Feng et al (2009)[66]	ABT-627, A-192621, or A-182086	Endothelin-A receptor antagonist, endothelin-B receptor antagonist, or a mixed endothelin receptor antagonist	50 mg/kg endothelin-A antagonist, 40 mg/kg endothelin-B antagonist, or 30 mg/kg mixed endothelin receptor antagonist once a day for 8 weeks during cirrhosis induction	Male BALB/c CCl_4-cirrhotic mice	Decreased portal pressure, fibrosis, α-SMA protein, and collagen I mRNA
Tsai et al (2018)[67]	Aleglizatar	Activation of PPARs	0·3 mg/kg per day for 12 weeks after thioacetamide administration in thioacetamide rats or 0·3 mg/kg per day for 3 weeks after cBDL for cBDL rats	Male Sprague–Dawley thioacetamide-cirrhotic rats and male Sprague–Dawley cBDL-cirrhotic rats	Decreased portal pressure, TNF-α, inflammation, hepatic fibrosis, and portosystemic shunt; improved systemic or splanchnic hyperdynamic circulation
Bravo et al (2021)[68]	Ambrisentan	Selective endothelin-receptor-A antagonist	2 mg/kg per day or 30 mg/kg per day for 2 weeks alone or in combination with 10 mg/kg per day of atorvastatin	Male Sprague–Dawley rats with MASH induced by high fat glucose-fructose diet	Decreased portal pressure, HVR, MASH score, and HSC contraction; improved markers of microvascular dysfunction
Trebicka et al (2007)[69]	Atorvastatin	KLF2 inducer	15 mg/kg once per day for 1 week	Male Sprague–Dawley cBDL-cirrhotic rats	Decreased portal pressure, fibrosis, apoptosis, protein expression, ECM, and HSC activation; increased PKG activity
Klein et al (2015)[70]	AVE 0991	Angiotensin-(1–7) receptor antagonist	1 mg/kg via the femoral vein during haemodynamic studies in CCl_4 rats, and osmotic mini pumps with AVE 0991 28 μg/kg per h for 2 weeks in cBDL rats	Male Sprague–Dawley CCl_4-cirrhotic and cBDL-cirrhotic rats	Decreased portal pressure and HVR

(Table 1 continues on next page)

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	Drug	Mechanism	Administration method	Experimental model	Effects
(Continued from previous page)					
Gao et al (2013)[71]	Celecoxib	COX-2 inhibitor	20 mg/kg per day by gavage starting from the initiation of thioacetamide administration for 16 weeks	Male Sprague–Dawley thioacetamide-cirrhotic rats	Decreased portal pressure, α-SMA, angiogenesis, and fibrosis; decreased mRNA expression of Col3A1, VEGF, COX-2, p-ERK, and PGE2
Schwabl et al (2021)[72]	Cilofexor	FXR agonist	10 or 30 mg/kg for 6 weeks and 9 weeks	Male Wistar choline-deficient high-fat diet MASH rats	Decreased portal pressure, MAP, hepatic fibrosis, Col1a1, HSC activation, and PDGFR-β
Lin et al (2017)[73]	LSECs-targeting COX-1 siRNA	COX inhibitor	Intravenous 0·6 mg/kg every other day from week 8 to week 12	Male C57BL/6 mice and CCl_4-cirrhotic rats injected for 12 weeks	Decreased portal pressure, thromboxane A2, thromboxane B2, and spleen size
Cerini et al (2016)[27]	Enoxaparin	Anticoagulant	1·8 mg/kg daily for 1 week (short term), daily for 3 weeks (long term), and daily for the last 3 weeks of cirrhosis induction (preventive)	Male Wistar CCl_4-cirrhotic or male Sprague–Dawley thioacetamide-cirrhotic rats	Decreased portal pressure, HVR, HSC activation, oxidative stress, liver microthrombosis, and fibrosis
Rodríguez-Vilarrupla et al (2012)[74]	Fenofibrate	PPAR-α agonist	25 mg/kg daily for 7 days	Male Wistar CCl_4-cirrhotic rats	Decreased portal pressure, HSC activation, hepatic fibrosis, and hepatic steatosis; increased MAP, nitric oxide bioavailability, and hepatic microvascular function
Traber et al (2013)[24]	GM-CT-01 and GR-MD-02	Galectin-3 inhibitor	60–180 mg/kg once per week for 4 weeks	Male Sprague–Dawley thioacetamide-cirrhotic rats	Decreased portal pressure, fibrosis, galectin-3-positive macrophages, HSC activation, portal inflammation, ballooning, collagen deposition, and iNOS expression
Boyer-Diaz et al (2021)[55]	Lanifibranor	Pan-PPAR agonist	100 mg/kg per day for 2 weeks	Male Sprague–Dawley thioacetamide or cBDL-cirrhotic rats	Decreased portal pressure, HVR, HSC activation, and liver fibrosis; improved LSEC phenotype; increased hepatic microvascular function
de Mesquita et al (2017)[56]	Liraglutide	GLP-1 receptor agonist	0·5 mg/kg per day for 15 days	Male Wistar thioacetamide-cirrhotic rats	Decreased portal pressure, liver fibrosis, and HSC activation; improved LSEC phenotype; increased hepatic microvascular function
Tripathi et al (2015)[28]	Metformin	Phosphorylated eNOS activity enhancer	300 mg/kg per day for 1 week	Male Wistar CCl_4-cirrhotic or Sprague–Dawley cBDL-cirrhotic rats	Decreased portal pressure, HVR, oxidative stress, and HSC activation; increased nitric oxide bioavailability
Fiorucci et al (2003)[75]	NCX-1000	Nitric oxide-releasing derivative of ursodeoxycholic acid	28 mg/kg per day for 5 days	Male Wistar cBDL-cirrhotic rats	Decreased portal pressure, HVR, and vasoconstriction; increased nitrite, nitrate, and cGMP
Verbeke et al (2014)[76]	Obeticholic acid	FXR agonist	30 mg/kg for 24 h and 4 h before the experiments (acute), and 30 mg daily or 5 mg/kg every 2 days for 10 days (chronic)	Male Wistar thioacetamide-cirrhotic or cBDL-cirrhotic rats	Decreased portal pressure and HVR; increased hepatic microvascular function and nitric oxide
Verbeke et al (2016)[77]	Obeticholic acid	FXR agonist	10 mg/kg every 2 days during the last 4 weeks of thioacetamide intoxication or every 2 days for 4 weeks after cirrhosis development	Male Wistar thioacetamide-cirrhotic rats	Decreased portal pressure, HVR, hepatic inflammation, fibrogenesis, LSEC, and Kupffer cell activation
Delgado et al (2013)[78]	ObR-Ab	Leptin receptor antagonist	8 μg/kg per day for 1 week	Male Wistar CCl_4-cirrhotic rats	Decreased portal pressure, HVR, and oxidative stress; increased cGMP
Wu et al (2022)[79]	Olmesartan	Angiotensin II receptor antagonist	5 mg/kg per day for 6 weeks	C57BL/6 CCl_4-cirrhotic mice	Decreased portal pressure, angiogenesis, HSC activation, and LSEC capillarisation; decreased expression of collagen IV, fibronectin, CD31, and vWF
Di Pascoli et al (2013)[80]	Resveratrol	Antioxidant	10 mg/kg per day and 20 mg/kg per day for 2 weeks	Male Wistar CCl_4-cirrhotic rats	Decreased portal pressure, thromboxane A2, liver fibrosis, desmin, and α-SMA; decreased expression of collagen I, TGF-β, and NFκB; and increased nitric oxide
Schwabl et al (2018)[81]	Riociguat	Soluble guanylate cyclase stimulator	Daily 1 mg/kg during the last 2 weeks in cBDL rats and during the last 3 weeks in CCl_4 rats	Male Sprague–Dawley cBDL-cirrhotic or CCl_4-cirrhotic rats	Decreased portal pressure, TNF-α, moesin and myosin expression, HSC α-SMA expression, ALT, AST, inflammation, and fibrosis; increased vasodilation
Vilaseca et al (2017)[82]	Rivaroxaban	Anticoagulant	20 mg/kg per day for 2 weeks	Wistar CCl_4-cirrhotic or Sprague–Dawley thioacetamide-cirrhotic rats	Decreased portal pressure, HSC activation, and liver microthrombosis; increased nitric oxide and LSEC phenotype
Guillaume et al (2013)[83]	Recombinant human manganese SOD	Antioxidant	15 μg/kg daily for 7 days	Male Wistar healthy, CCl_4-cirrhotic, or cBDL-cirrhotic rats	Decreased portal pressure, HVR, oxidative stress, and deposition of fibrillar collagen; increased vasorelaxation
Lee et al (2010)[84]	Sildenafil	PDE5 inhibitor	0·25 mg/kg twice a day for 1 week	Male Sprague–Dawley cBDL-cirrhotic rats	Decreased portal pressure; increased nitric oxide, phosphorylated eNOS, and Akt phosphorylation

(Table 1 continues on next page)

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	Drug	Mechanism	Administration method	Experimental model	Effects
(Continued from previous page)					
Abraldes et al (2007)[85]	Simvastatin	KLF2 inducer	25 mg/kg per day for 3 days	Male Wistar CCl_4-cirrhotic rats	Decreased portal pressure and increased phosphorylated eNOS and LSEC function
Huang et al (2010)[60]	Simvastatin	KLF2 inducer	20 mg/kg per day from day –2 to day +7 of ligation	Male Sprague–Dawley rats with portal hypertension induced by PPVL	Decreased portal pressure and collateral vascular resistance; increased scavenger receptor, phosphorylated eNOS, COX-2, and thromboxane A2 expression
Hsu et al (2013)[86]	Simvastatin	KLF2 inducer	20 mg/kg per day from day –2 to day +7 of ligation	Male Sprague–Dawley rats with portal hypertension induced by PPVL	Decreased portal pressure and collateral vascular resistance
Wang et al (2013)[87]	Simvastatin	KLF2 inducer	4 mg/kg per day for 8 weeks	Male Wistar rats with MASLD induced by high-fat diet	Decreased iNOS and collagen I, and increased phosphorylated eNOS
La Mura et al (2013)[59]	Simvastatin	KLF2 inducer	25 mg/kg per day starting 3 days before lipopolysaccharide injection	Male Wistar rats	Decreased portal pressure and LSEC dysfunction, and increased eNOS phosphorylation
Meireles et al (2017)[88]	Simvastatin	KLF2 inducer	5 mg/kg per day starting 3 days before the experiments	Male Sprague–Dawley cBDL-cirrhotic rats subject to haemorrhage and resuscitation	Decreased vasoconstriction, ALT, AST, and expression of inflammatory genes
Maeso-Díaz et al (2019)[89]	Simvastatin	KLF2 inducer	5 mg/kg per day for 15 days	20-month-old male Wistar CCl_4-cirrhotic rats	Decreased portal pressure, HVR, LSEC dysfunction, HSC activation, and fibrosis
Bravo et al (2019)[90]	Simvastatin; atorvastatin	KLF2 inducers	10 mg/kg per day for 2 weeks	Male Sprague–Dawley rats with MASLD induced by a high fat glucose-fructose diet	Decreased portal pressure, LSEC dysfunction, and HSC activation; increased eNOS and Akt phosphorylation
Mejias et al (2009)[91]	Sorafenib	Multikinase inhibitor	2 mg/kg per day for 2 weeks in PPVL rats, and 1 mg/kg per day for 2 weeks in cBDL-cirrhotic rats	Male Sprague–Dawley PPVL or cBDL-cirrhotic rats	Decreased portal pressure (cBDL), splanchnic neovascularisation, inflammation, liver damage, liver fibrosis, and angiogenesis
Zheng et al (2022)[92]	Telmisartan	PPAR-γ agonist and angiotensin receptor blocker	10 mg/kg per day from the first day for 4 weeks for cBDL rats, and from the 12th week for 4 weeks for CCl_4 rats	Male Sprague–Dawley CCl_4-cirrhotic and cBDL-cirrhotic rats	Decreased portal pressure, MAP, phosphorylated eNOS, and angiogenesis; decreased mRNA expression of MMP-2, MMP-9, VEGF, vWF, PDGF-β, TFG-β, α-SMA, and Col1a1; and increased KLF-4
Rosado et al (2013)[93]	Terutroban	Thromboxane receptor antagonist	30 mg/kg per day for 2 weeks	Male Wistar CCl_4-cirrhotic rats	Decreased portal pressure, HVR, and fibrosis; decreased collagen I and TGF-β mRNA; decreased α-SMA protein
Choi et al (2009)[94]	Udenafil	PDE5 inhibitor	1 mg/kg per day, 5 mg/kg per day, or 25 mg/kg per day for 3 weeks or 4 weeks	Male Sprague–Dawley cBDL-cirrhotic rats	Decreased portal pressure, fibrosis, pro-collagen type I, and α-SMA

Therapeutic strategies are classified according to their duration (short-duration or long-duration administration). α-SMA=α-smooth muscle actin. ALT=alanine aminotransferase. AST=aspartate aminotransferase. cBDL=common bile duct ligation. cGMP=cyclic GMP. CCl_4=carbon tetrachloride. COX=cyclooxygenase. CTGF=connective tissue growth factor. ECM=extracellular matrix. eNOS=endothelial nitric oxide synthase. FXR=farnesoid X receptor. HSC=hepatic stellate cell. HVR=intrahepatic vascular resistance. iNOS=inducible nitric oxide synthase. KLF=Krüppel-like factor. LSEC=liver sinusoidal endothelial cell. MAP=mean arterial pressure. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. MMP=matrix metalloproteinase. NF-κB=nuclear factor-κB. PDE5=phosphodiesterase type 5. PDGF=platelet-derived growth factor. PDGFR=platelet-derived growth factor receptor. PGE2=prostaglandin E2. PKG=protein kinase G. PPAR=peroxisome proliferator-activated receptor. p-ERK=phosphorylated extracellular signal-regulated kinase. PPVL=partial portal vein ligation. SOD=superoxide dismutase. TGF-β=transforming growth factor-β. TNF-α=tumour necrosis factor-α. VEGF=vascular endothelial growth factor. vWF=von Willebrand factor.

Table 1: **Preclinical evidence for pharmacological interventions targeting intrahepatic dysregulations in portal hypertension**

the availability of more effective alternatives.[124] Conversely, nitric oxide enhancers have been extensively characterised and research is shifting focus onto enhancing the effects of nitric oxide downstream as a pharmaceutical strategy. Nitric oxide mediates the synthesis of cyclic GMP in HSCs via activity of soluble guanylate cyclase, which ultimately promotes cell relaxation. However, in chronic liver disease, increases in the enzymatic activity of phosphodiesterase type 5 (PDE5) triggers cyclic GMP degradation, which contributes to the development of vasoconstriction and microvascular dysfunction.[125] Therefore, the use of PDE5 inhibitors or soluble guanylate cyclase stimulators might ameliorate portal hypertension.[62,81]

Targeting vasoconstrictors

Inhibitors of angiotensin II receptors have been tested as anti-vasoconstriction therapies to revert the effect of angiotensin II and consequently promote the vasodilatation of hepatic circulation.[126] For instance, olmesartan and valsartan have shown, in preclinical and clinical studies, an inhibitory effect on vasoconstriction and vasoconstriction-promoted sinusoidal remodelling.[79,107,127]

Endothelin-A and endothelin-B are the two main G protein-coupled receptors of endothelin, a vasoactive molecule produced by the endothelium. The interaction of endothelin with each receptor triggers different responses. When endothelin interacts with endothelin-A receptor, vasoconstriction is induced, whereas the interaction with

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	Drug	Mechanism	Dose	Population	Effects
Short-duration with positive effects					
Zipprich et al (2021)[95]	Ambrisentan	Endothelin-A receptor antagonist	5 mg or 10 mg single oral administration	14 patients with cirrhosis who underwent TIPS evaluation	Decreased HVPG and MAP
Hernández-Guerra et al (2006)[96]	Ascorbic acid	Antioxidant	One intravenous dose of 3 g followed by a standard liquid meal	37 patients with portal hypertension and cirrhosis	Decreased HVPG, malondialdehyde, and endothelial dysfunction
Zipprich et al (2021)[95]	BQ-123	Endothelin-A receptor antagonist	Increasing doses of 300 nmol/L, 500 nmol/L, 1000 nmol/L, and 2000 nmol/L infused through the hepatic artery	26 patients were included, 12 patients in substudy 1 (local administration and infused into the hepatic artery) and 14 patients in the substudy 2 (systemic administration and oral administration)	Vasodilation of the hepatic artery, decreased portal pressure and HVPG, and increased hepatic arterial blood flow
Bellis et al (2003)[97]	Isosorbide mononitrate	Nitric oxide donor	Single oral dose of 10 mg 5-isosorbide mononitrate and a standard liquid meal 15 min later	23 patients with cirrhosis and portal hypertension	Decreased portal pressure, HVPG, and MAP
Rittig et al (2021)[98]	Metformin	Phosphorylated eNOS activity enhancer	One oral dose of 1000 mg	32 patients with cirrhosis	Decreased HVR
Zafra et al (2004)[99]	Simvastatin	KLF2 inducer	40 mg received orally at 24 h and 60 min before the study	30 patients with cirrhosis and HVPG ≥12 mm Hg	Decreased HVR, and increased hepatic blood flow and nitric oxide concentrations
Zhang et al (2013)[100]	Somatostatin	Growth hormone inhibitor	250–500 μg/h bolus plus continuous infusion of 250–500 μg/h	41 patients with chronic viral hepatitis or alcohol-related cirrhosis	Decreased portal pressure
Deibert et al (2006)[101]	Vardenafil	PDE5 inhibitor	A single oral dose of 10 mg	18 patients with Child–Pugh class A liver cirrhosis	Decreased portal pressure and increased portal blood flow
Long-duration with positive effects					
Mookerjee et al (2014)[102]	Obeticholic acid	FXR agonist	10 mg or 25 mg orally each day for 7–12 days	25 patients with alcohol-related cirrhosis and portal hypertension	Decreased HVPG
Abraldes et al (2009)[103]	Simvastatin	KLF2 inducer	20 mg/day orally for 15 days and then 40 mg/day for 15 days	59 patients with cirrhosis and portal hypertension	Decreased HVPG and increased liver perfusion and function
Abraldes et al (2016)[104]	Simvastatin	KLF2 inducer	20 mg/day orally for 15 days and 40 mg/day thereafter for 2 years	158 patients with cirrhosis who had recovered from variceal bleeding	Increased survival and liver function
Schwarzer et al (2018)[105]	Taurine	Anti-fibrotic	6 g/day orally for 4 weeks	22 patients with HVPG ≥12 mm Hg	Decreased HVPG
Kreisel et al (2015)[106]	Udenafil	PDE5 inhibitor	12·5 mg/day, 25 mg/day, 50 mg/day, 75 mg/day, or 100 mg/day orally for 1 week	35 patients with compensated liver cirrhosis and HVPG ≥12 mm Hg	Decreased HVPG and MAP
Huo et al (2009)[107]	Valsartan	Angiotensin II receptor antagonist	80 mg/day orally for 1 month	36 patients with cirrhosis	Decreased portal pressure; decreased CGRP, hyaluronic acid, cholylglycine, and PAI-1 in blood; decreased diameter of and increased blood velocity in the portal and splenic vein
Pinter et al (2012)[108]	Sorafenib	Multikinase inhibitor	400 mg orally twice daily for 2 weeks	13 patients with CLD fibrosis or cirrhosis and hepatocellular carcinoma	Decreased HVPG and decreased expression of VEGF, PDGF, PlGF, RhoA kinase, and TNF-α
Negative studies					
Chalasani et al (2020)[109]	Belapectin	Galectin-3 inhibitor	Infusions of 2 mg/kg or 8 mg/kg received once every 2 weeks for 52 weeks	162 patients with MASH, cirrhosis, and portal hypertension	No significant effect on patients with oesophageal varices
Tripathi et al (2006)[110]	BQ-123	Endothelin-A receptor antagonist	1 μmol/min and 3 μmol/min infused for 20 min	16 patients with cirrhotic portal hypertension	No effects on HVPG; decreased MAP and pulmonary vascular resistance
Garcia-Tsao et al (2020)[111]	Emricasan	Pan-caspase inhibitor	Twice daily oral emricasan 5 mg, 25 mg, 50 mg for up to 48 weeks	263 patients with MASH-related cirrhosis and HVPG ≥12 mm Hg	No significant differences in HVPG in all groups versus placebo at 24 weeks; decreased HVPG in the subgroup of more severe portal hypertension
Berzigotti et al (2010)[112]	NCX-1000	Nitric oxide-releasing derivative of ursodeoxycholic acid	Progressive oral doses of up to 2 g three times a day or maximum tolerated dose for 16 days	11 patients with cirrhosis and portal hypertension	No effects on HVPG; lack of selective release of nitric oxide at the intrahepatic circulation
Kimer et al (2017)[113]	Rifaximin	Non-systemic antibiotic	550 mg twice a day orally for 4 weeks	54 stable outpatients with cirrhosis and ascites	No effects on HVPG, concentrations of vasoactive hormones, or systemic haemodynamics

(Table 2 continues on next page)

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	Drug	Mechanism	Dose	Population	Effects
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Reverter et al (2015)[114]	Sapropterin (analogue of BH_4)	Phosphorylated eNOS activator	5 mg/kg per day increased to 10 mg/kg per day orally at day 8 for 2 weeks in total	40 patients with cirrhosis and portal hypertension	No effects on HVPG and endothelial dysfunction markers; liver function tests remained unchanged
Gifford et al (2020)[115]	Serelaxin (recombinant human relaxin-2)	Anti-fibrotic	Infusion of 80 µg/kg per day for 60 min followed by 30 µg/kg per day for at least 60 min for 4 weeks	17 patients with cirrhosis and portal hypertension	No effects on HVPG and systemic haemodynamics
Clemmesen et al (2008)[116]	Sildenafil	PDE5 inhibitor	Oral administration of 50 mg single dose	10 patients with biopsy-proven cirrhosis and portal hypertension	No influence on splanchnic blood flow, oxygen consumption, or HVPG; decreased MAP

Therapeutic strategies are classified according to their therapy duration and effects (positive effects on portal hypertension or non-response). CGRP=calcitonin gene-related peptide. CLD=chronic liver disease. eNOS=endothelial nitric oxide synthase. FXR=farnesoid X receptor. HVPG=hepatic venous pressure gradient. HVR=intrahepatic vascular resistance. KLF=Krüppel-like factor. MAP=mean arterial pressure. MASH=metabolic dysfunction-associated steatohepatitis. PAI-1=plasminogen activator inhibitor-1. PDE5=phosphodiesterase type 5. PDGF=platelet-derived growth factor. PIGF=placental growth factor. TIPS=transjugular intrahepatic portosystemic shunt. TNF-α=tumour necrosis factor-α. VEGF=vascular endothelial growth factor.

Table 2: **Clinical evidence for pharmacological interventions targeting intrahepatic dysregulations in portal hypertension**

endothelin-B receptor primarily causes the release of the vasodilator nitric oxide. However, in a cirrhotic liver, the concentration of endothelin-A receptor is higher than that of endothelin B receptor.[95] For this reason, most therapeutic strategies targeted at endothelin receptors focus on inhibiting endothelin-A receptor to reduce vasoconstriction.[95]

Furthermore, the cyclooxygenase-mediated molecular pathway plays a key role in portal hypertension, mediating HSC contraction, and therefore offers the rationale to inhibit cyclooxygenase,[53] cysteinyl leukotrienes,[128] and prostanoids[54] to treat portal hypertension.

Antioxidants

The overproduction and accumulation of reactive oxygen species within a cirrhotic liver promotes cell damage and, importantly, leads to a reduction in nitric oxide bioavailability and consequently increases the hepatic vascular tone.[129] Recombinant human manganese superoxide dismutase has been used in a preclinical rat model with cirrhosis and portal hypertension and significantly reduced intrahepatic vascular resistance, portal pressure, and liver fibrosis by improving endothelial function.[83] Apart from drugs with antioxidant properties, antioxidant nutraceuticals and natural products have been used to treat portal hypertension and cirrhosis in animal models. Specifically, the nutraceuticals resveratrol and docosahexaenoic acid reduced portal pressure, increased nitric oxide production, and improved endothelial dysfunction in cirrhotic rats.[80,130] In humans with cirrhosis, the consumption of dark chocolate showed a mitigating effect on the postprandial elevation of HVPG.[131] This effect was attributed to the enhancement of flow-mediated hepatic vasorelaxation coupled with the concurrent amelioration of systemic hypotension.[131] Furthermore, ascorbic acid enhanced intrahepatic endothelial function in patients with cirrhotic portal hypertension, thereby attenuating the postprandial elevation in HVPG.[96] Therefore, the amelioration of oxidative stress by reducing reactive oxygen species by use of antioxidant therapies is an important line of inquiry in the treatment of portal hypertension.

Anticoagulants

In the context of chronic liver disease, the factors contributing to the advancement of the disease are those that result in elevated vascular tone. One of these factors is thrombosis, which leads to vascular blockage, affecting sinusoids and hepatic veins. This obstruction causes tissue congestion, resulting in focal necrosis, referred to as parenchymal extinction. Consequently, thrombosis emerges as an important factor in the decompensation of liver disease, causing the loss of contiguous hepatocyte regions and the impairment of local microvasculature.[132] Anticoagulants have been studied as a therapeutic option against portal hypertension due to their effect of modulating vascular alterations, such as endothelial injury and occlusion of small hepatic vessels that can cause tissue collapse and architectural distortion (eg, micro-thrombi in the hepatic circulation), thus reverting the parenchymal extinction sequence.[132] Moreover, anticoagulants would have independent antifibrotic effects, as their administration in preclinical models of cirrhosis in vivo and in vitro ameliorated a HSC phenotype and hepatic fibrosis.[82] Indeed, a small randomised controlled trial showed that enoxaparin prevented portal vein thrombosis in patients with cirrhosis and seemed to delay hepatic decompensation and improve survival.[133] A 2023 meta-analysis also showed that anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis.[134]

Antifibrotics

Antifibrotics have been evaluated for their ability to ameliorate structural changes and reduce extracellular matrix deposition in cirrhotic portal hypertension. These structural alterations are mainly induced by HSC activation, which is responsible for liver fibrogenesis. Hence, studies have been conducted with the aim of finding therapeutic strategies for HSC deactivation

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with the objective of reducing portal hypertension. Anti-inflammatory and antioxidant drugs have shown antifibrotic properties that result in reduced HSC activation and hepatic fibrosis, including GLP-1 receptor agonists,[56] galectin-3 inhibitors,[109] antibodies against leptin receptors,[78] and Rho kinase inhibitors.[135]

Interventional procedures for portal hypertension

Interventional procedures have typically been considered as a last resort in the management of portal hypertension. In situations in which pharmacological therapies do not yield clear benefits, such as in patients with CSPH who are unresponsive to treatment, a transjugular intrahepatic portosystemic shunt (TIPS) might be recommended.[136] Via the internal jugular vein, a hepatologist or interventional radiologist establishes an intrahepatic shunt between a hepatic arteriole and a vein within the liver by perforating the tissue and introducing an expandable metal stent, effectively bypassing the hepatic microcirculation and its associated resistance. Adding the stent results in the establishment of an alternative path for a portion of the hepatic blood flow, leading to an immediate reduction in portal pressure. TIPS has been reported to lower portal pressure to less than the thresholds of 12 mm Hg and 10 mm Hg, effectively eliminating the risk of further complications associated with portal hypertension, such as portal vein thrombosis, variceal bleeding, hepatic hydrothorax, and hepatorenal and hepatopulmonary syndromes.[136] In addition, TIPS has been proposed as an alternative to large-volume paracentesis, as CSPH associated with refractory ascites has been shown to significantly improve within 6–12 months after TIPS, resulting in reduced sodium retention and improved renal function.[137] In fact, the application of TIPS for refractory ascites and as a preventive measure against variceal rebleeding diminishes the occurrence of subsequent decompensation events compared with standard of care.[138] Additionally, TIPS enhances survival rates, particularly in carefully selected patients, which is the key to elective TIPS.[138] Furthermore, this intervention is minimally invasive and highly effective compared with other shunting techniques.[136,139] However, it is important to note that TIPS is not a curative treatment for chronic liver disease and does not stop the progression of the disease. Hence, pre-emptive TIPS is indicated for patients at high risk of not responding to standard therapy to treat acute variceal haemorrhage. Non-pre-emptive TIPS is used as a second-line therapy for the prevention of recurrent variceal haemorrhage and for the treatment of ascites.[136,140] Additionally, the proportion of blood that circumvents the liver, as observed in cases of pathological portosystemic circulation, might still contribute to the development of recurrent episodes of hepatic encephalopathy without an identifiable precipitating factor, heart failure, or portal and pulmonary hypertension.[136]

Splenomegaly is a consequence of portal hypertension or portal vein obstruction, and a factor contributing to the hyperdynamic circulation.[141] It is worth noting that the blood flow from the spleen can contribute to as much as 30% of the total volume of blood in the portal vein, thereby majorly increasing portal pressure.[142] A preclinical study evaluated the role of splenectomy as an interventional approach for portal hypertension in rats.[142] The authors suggest that splenectomy reduced the rate of fibrosis development in the studied preclinical models, and attenuated the decrease in mean arterial pressure. Furthermore, partial or total splenectomy induced a reduction in portal blood flow, subsequently leading to improved portal hypertension. In humans, retrospective studies assessing patients with cirrhosis undergoing splenectomy also show improvement in portal hypertension and intrahepatic vascular resistance.[143] However, there is controversy around the safety and efficacy of this interventional approach for the treatment of portal hypertension as it has also been associated with adverse events, such as portal vein thrombosis, surgical bleeding, sepsis, increased splenic vein diameter, and lower white blood cell count.[144,145] Therefore, splenectomy is not recommended in any clinical guidelines.

The last option for chronic liver disease is liver transplantation, which remains the most effective treatment for advanced chronic liver disease with decompensated liver function.[144,146] High mortality for those on the liver transplant waiting list, organ shortages, and high medical costs are the major problems of liver transplantation. Pre-emptive TIPS helps in controlling severe variceal bleeding, improving survival for patients on the liver transplant waiting list, especially those with high HPVG.[136] Moreover, it is reported that TIPS does not impede subsequent liver transplantation, which supports the use of TIPS before liver transplantation, even in patients with decompensation.[147] However, when selecting candidates for TIPS in the context of liver transplantation, there are some contraindications to this interventional strategy, such as the primary prevention of variceal bleeding, congestive heart failure, severe tricuspid regurgitation, multiple hepatic cysts, uncontrolled systemic infection or sepsis, unrelieved biliary obstruction, and pulmonary arterial pressure of more than 45 mm Hg. TIPS placement is not indicated for patients with these features; they will not have any alternative or bridging therapy before liver transplantation. However, approximately 14% of individuals requiring liver transplantation will initially undergo TIPS placement.[148]

Novel interventions targeting specific liver cell types

There is an unmet need to develop more powerful and specific antifibrotic strategies with fewer side-effects. Therefore, new therapeutic options to specifically deliver drugs or antifibrotic factors directly to a target cell type are being developed. Thanks to advances in bioengineering, it is now possible to produce nanoparticles or nanocarriers for drug delivery with chemical properties that protect their cargo against premature degradation and enhance

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biological stability. Nanoparticles and nanocarriers allow for the attachment of biorecognition patterns for cell-specific targeting, which results in generally better efficacy and increased drug delivery compared with traditional drug administration methods.[64,149] For example, the delivery of nitric oxide by nanoparticles coated with vitamin A to target HSCs attenuated HSC contraction and inhibited collagen I and α-smooth muscle actin expression to reduce portal pressure in a cBDL rat model of cirrhosis.[64] Moreover, the oral administration of valsartan loaded in vitamin A-coupled liposomes reduced fibrogenesis in cirrhotic rats.[63] Therefore, research into new interventions has been directed towards liver-selective drugs with demonstrated efficacy for the treatment of portal hypertension.

New research focus and methods

Sharing RNA sequencing data

In recent years, there has been a considerable increase in the use of RNA sequencing techniques, which have provided valuable insights into liver pathobiology. RNA sequencing has enabled the comprehensive profiling of gene expression within liver tissues from numerous patients, which has facilitated the characterisation of dysregulated genes and pathways implicated in chronic liver disease and portal hypertension.[150,151] Of note, the open publication of these data has facilitated use across research centres, resulting in a fast growth of translational research in the field.

Single-cell RNA sequencing and single-nuclei RNA sequencing have allowed for the characterisation of different cell subpopulations within tissues. Although these techniques might not be currently suitable for routine application on patient samples due to the substantial amount of tissue required, cost, and technical skills, the existence of public databases (such as the National Institutes of Health Gene Expression Omnibus or dedicated databases from the authors of single-cell RNAseq papers) hosting these sequencing data allows for efficient and prompt exploration of gene expression patterns among various cell types. The combination of single-cell RNA sequencing with spatial transcriptomics and known transcriptional patterns has provided a means to analyse gene expression in correlation with the spatial arrangement of cells within tissues and, therefore, the identification of gene expression patterns for cell subtypes along the sinusoid (eg, liver sinusoidal endothelial cells [LSECs] adjacent to the central vein or the portal vein).[152] The use of these techniques together with conventional bulk RNA sequencing presents a powerful, accessible, and straightforward workflow for generating novel and unbiased hypotheses for translational studies in the field of chronic liver disease and portal hypertension.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "portal hypertension", "therapies against portal hypertension", "pathophysiology of portal hypertension", and "mechanisms of portal hypertension" from Jan 1, 1995, to Oct 31, 2023. Articles were also identified via searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Animal models of cirrhotic portal hypertension

Conventional animal models of portal hypertension are still widely used. The partial portal vein ligation model involves surgically constricting the portal vein in rats and mice, rendering it a suitable method for investigating portal hypertension, especially its extrahepatic pathophysiology, in the absence of cirrhosis. By contrast, rat and mouse models of chronic liver disease, such as bile duct ligation, CCl_4 inhalation or injection, and thioacetamide administration, all induce portal hypertension associated with cirrhosis. The bile duct ligation model is generated by surgically ligating (and sometimes resecting) the bile duct, resulting in chronic liver damage due to the accumulation of bile. Given that removing the ligation involves a second surgery, with collateral veins in the vicinity, removal of the causal agent in this model is more difficult than in models generated by the administration of a toxicant, such as CCl_4 and thioacetamide. Consequently, CCl_4 and thioacetamide models prove more fitting for the exploration of cirrhosis regression. Nevertheless, it is generally acknowledged that these models bear a closer phenotypical resemblance to human alcohol-related cirrhosis rather than MASLD, primarily due to the absence of steatohepatitis in these animals. The high prevalence of MASLD in the human population has prompted the search for suitable models of chronic liver disease that display both the distinctive features of MASLD and portal hypertension.

The methionine-deficient and choline-deficient diet mouse model is capable of replicating both steatohepatitis (encompassing steatosis and fibrosis) and portal hypertension.[153] Compared with other diet-induced disease models (eg, the high-fat diet model), the methionine-deficient and choline-deficient diet model is better at achieving fibrosis and portal hypertension.[153] However, an important drawback of this model is that these animals have weight loss, which suggests that the extrahepatic phenotype greatly diverges from metabolic dysfunction-associated steatohepatitis in humans. This need for better suited models has led to the description of newer animal models of chronic liver disease and portal hypertension that involve a two-step injury process.[153] Initially, steatosis is generated with a high-fat diet and this injury is then followed by the administration of a profibrotic stimulus, or vice versa, resulting in the eventual development of portal hypertension.[153]

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New mechanical players in the pathophysiology of portal hypertension

Isolating liver cells from animals with portal hypertension allows for the preclinical assessment of cellular phenotypes in chronic liver disease. However, to enhance the translatability of in-vitro studies, precision-cut liver slices provide a valuable platform for assessing human liver tissue in an ex-vivo environment.[154] This approach preserves the three-dimensional structure of cells and their interactions with both neighbouring cells and the extracellular matrix.[154] Modern in-vitro culture techniques have also evolved to enable the controlled regulation of biomechanical stimulation, including hydrodynamic pressure. With these techniques, a precise examination of the specific effect of portal hypertension on liver cells can be achieved. In a 2023 study, our team used a custom-designed organ-on-a-chip device to expose primary LSECs to varying pressure gradients, representing both normal and pathological conditions.[155] This exposure to increased pressure prompted changes in LSEC transcriptomic profiles reminiscent of those observed in cirrhosis, ultimately proposing novel biomarkers of portal hypertension.[155] Similarly, Hilscher and colleagues used a distinct device configuration to subject mouse LSECs to stretching, mimicking the mechanical forces in vessels due to elevated pressure and resulting in a prothrombotic phenotype.[156] Other mechanical forces, such as shear stress or substrate stiffness, which are related to hydrodynamic pressure in vivo, can be recapitulated in vitro, driving the cellular phenotype of liver cells.[12] Indeed, in a 2020 study, we found that increased stiffness of the matrix substrate (which could be derived from fibrosis, but also from increased turgor due to elevated pressure) modified the phenotype of the main hepatic cell types (LSECs, HSCs, and hepatocytes) derived from rats.[157] Conversely, reducing the substrate stiffness induced an improvement in the phenotype of parenchymal and non-parenchymal cells,[157] suggesting that mechanical forces could play a determinant role in the regression of fibrosis and portal hypertension.

This collective body of research highlights the growing capability of in-vitro techniques to replicate and investigate the cellular responses to elevated pressure associated with portal hypertension.

Conclusion

Portal hypertension represents a multifaceted pathological hallmark observed in advanced stages of chronic liver disease. It is well documented that the development of hepatic microcirculatory dysfunction results from a complex interplay of various structural and haemodynamic mechanisms, collectively contributing to vasoconstriction of the hepatic sinusoids, cellular dedifferentiation, deposition of extracellular matrix, and endothelial capillarisation. Therefore, a comprehensive understanding of the fundamental pathophysiological mechanisms of portal hypertension will help the advancement and establishment of innovative therapeutic approaches in its management. Several therapeutic interventions have shown the ability to mitigate portal hypertension, thereby alleviating the hepatic burden arising from structural alterations and enhanced hepatic vascular tone in both preclinical and clinical models. Nonetheless, additional research efforts are warranted in the pursuit of novel and promising delivery strategies that directly target sinusoidal cells. Such advances are imperative to mitigate drug non-specificity and cytotoxicity, thereby reducing the likelihood of adverse effects stemming from both systemic and intrahepatic therapeutic modalities.

Contributors

SG-M and SQ-V performed the literature review and conceptualised and wrote the manuscript. JG-S conceptualised, coordinated the writing, and critically reviewed and edited the manuscript.

Declaration of interests

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